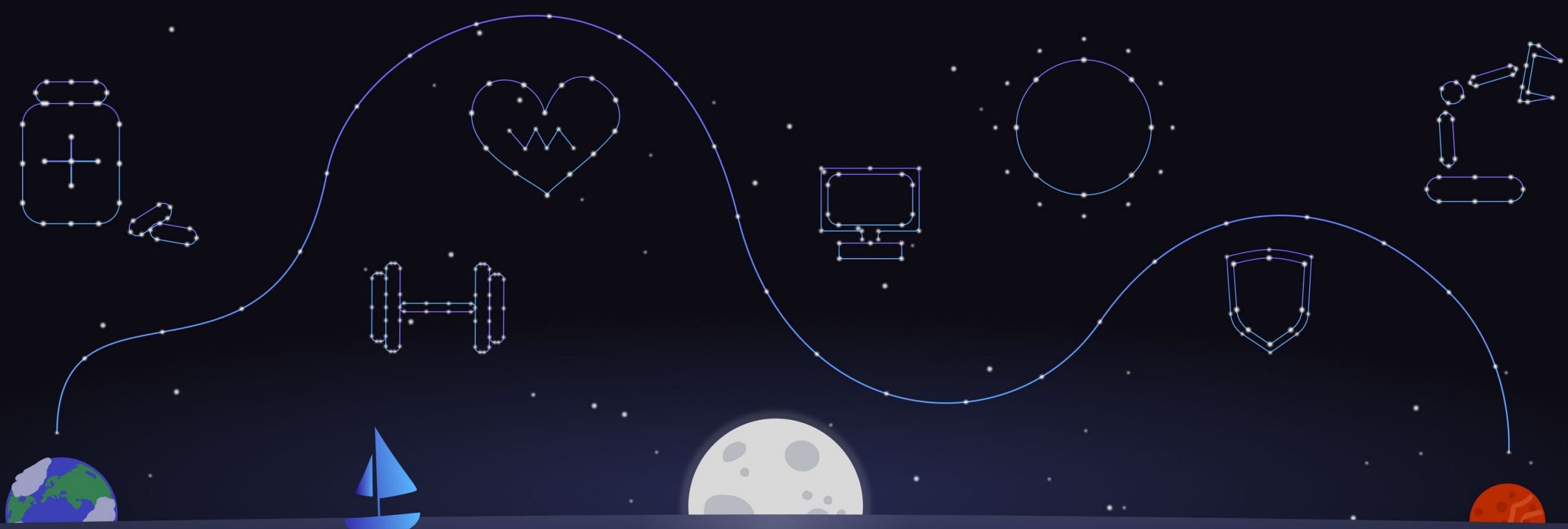

Risk of Exposure Induced Death Associated with Clonal Hematopoiesis of Indeterminate Potential for Mars Mission Scenarios

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*Disclaimer: This work was prepared while Z.S. Patel was employed at KBR/NASA JSC. The opinions expressed in this work are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government

CHIP

Clonal Hematopoiesis of Indeterminate Potential

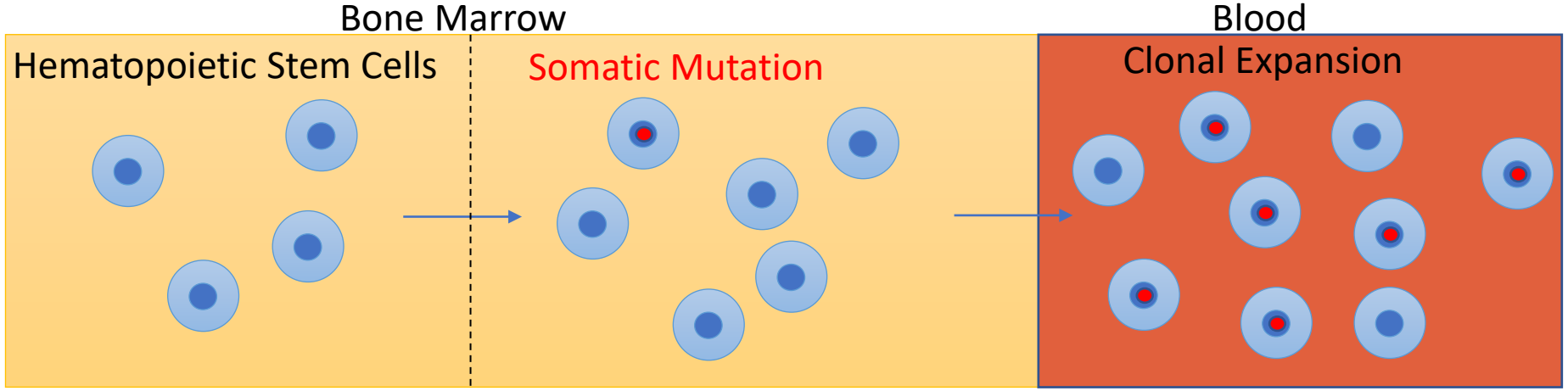


Figure adapted from Mooney et al. *Clin. Sci. (Lond)* (2021) 135 (7): 991-1007.

Radiation Exposure?

Hypothesis: Radiation Related Leukemia is mainly attributable to those who carry pre-existing clonally expanded preleukemic cells
Nakamura, *Radiation Res*. 163, 258-265 (2005).

CHIP Ties to Leukemia and Cardiovascular Disease (CVD)
Jaiswal et al. *N Engl J Med.* (2014) 371 (26): 2488-2498.

Statistically significant increases in incident coronary heart disease (CHD), ischemic stroke, and leukemia

(Cohort size: 17,182 persons)

	Hazard Ratio	95% Confidence Limit
*Leukemia	11.1	[3.9, 32.6]
CHD	2.0	[1.2, 3.4]
Ischemic Stroke	2.6	[1.4, 4.8]
All Cause Mortality	1.4	[1.1, 1.8]

*Leukemia : NASA Space Cancer Risk Model (NSCR) uses blood forming organs (bfo), where Leukemia originates

Risk of Exposure Induced Death

$$\mathrm{REID}_T = \int_{a_E}^{a_{\max}} \lambda_T^M(a, a_E, \nu_T, H_T, \Delta_T) S_0(a|a_E) e^{-\sum_{T'} \int_{a_E}^{a} \lambda_{T'}^M(t, a_E, \nu_{T'}, H_{T'}, \Delta_{T'}) dt} da$$

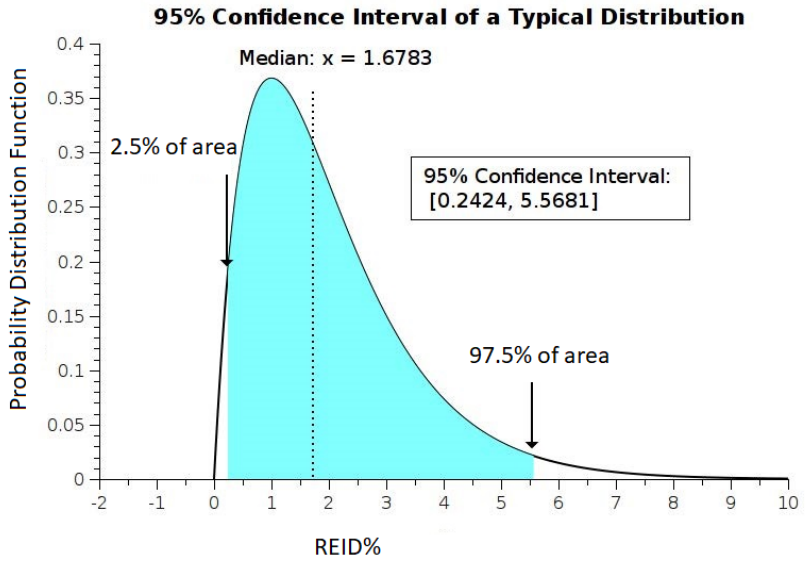
$\lambda_T = \nu_T \mathrm{ERR}_T \lambda_{0,T} + R_T^M(a)(1-\nu_T)\mathrm{EAR}_T$

Conditional probability of survival for background population (no excess radiation exposure)

Competing causes of death due to radiation exposure

Background mortality rates, which include cancer, stroke, and CHD

ERR = Excess Relative Risk
EAR = Excess Absolute Risk



NASA STD-3001

"Career exposure to radiation is limited to not exceed 3 percent Risk of Exposure Induced death (REID) for fatal cancer. NASA assures that this risk limit is not exceeded at a 95 percent confidence level…"

Objective

- Perform **sensitivity analysis** on REID by modification of background mortality rates with CHIP hazard ratios from Jaiswal et al. *N Engl J Med.* (2014) 371 (26): 2488-2498
- Evaluate possibility of **inflight risk**
- Evaluate **long term risk** and provide motivation for increased screening
- **Case studies informed by flight surgeons** to assess how to move toward more **personalized information** in risk calculations that could be used for **medical management**

*** This analysis will NOT be used for selection to astronaut program (for employment) in compliance with US Genetic Information Nondiscrimination Act (GINA) laws.**

Space Environment and Assumptions

Mars Design Reference Mission (DRM) Parameters

- 12-month transit to Mars
- 1-month stay on Martian Surface
- 9-month return transit

Space Radiation Environment

- 2001 Galactic Cosmic Ray (GCR) as modeled by Badhwar O'Neill (2014) at solar maximum
- August 1972 Solar Particle Event (SPE) as modeled by King
- 9-month International Space Station (ISS) Exposure
- Male Adult voXel and Female Adult voXel human phantom models

CHIP Assumptions in NASA Space Cancer Risk Model (NSCR)

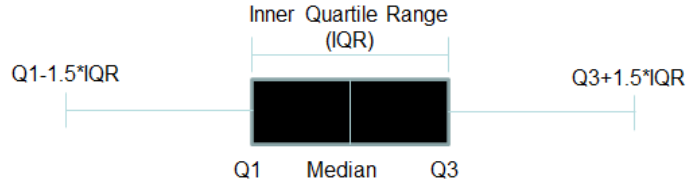
- CHIP mortality rates are assumed to be proportional to incidence rates
- Background mortality modifications are applied from exposure age to end of life

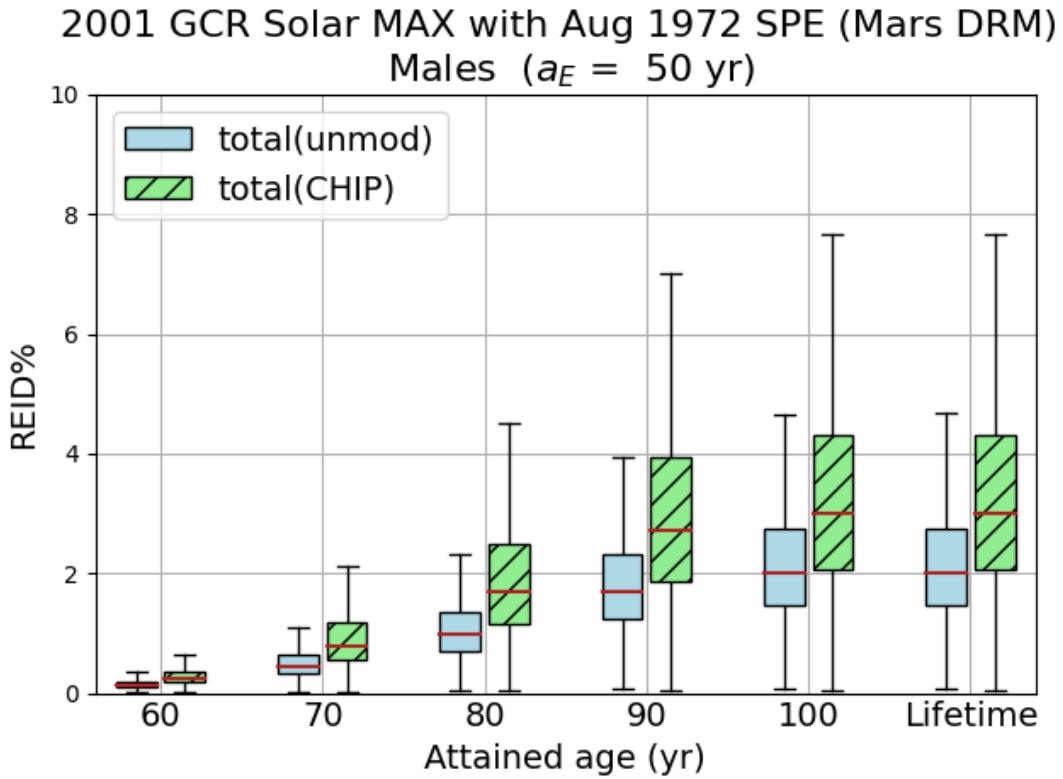
Astronaut Scenarios

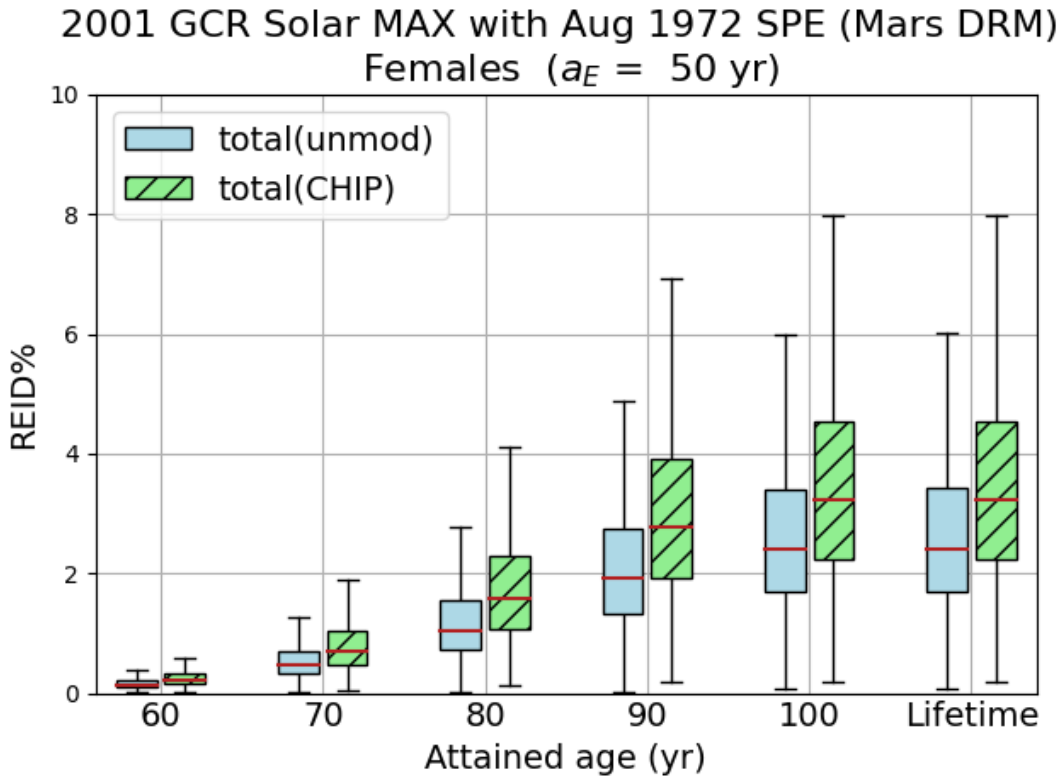
Case 1: 50 yr old males and females exposed to GCR and SPE environments for Mars DRM Scenario with no previous radiation exposure from ISS

Case 2: 50 yr old males and females exposed to GCR and SPE environments for Mars DRM Scenario with previous ISS exposure at age 28

Case 1: Mars Mission without Previous Exposure

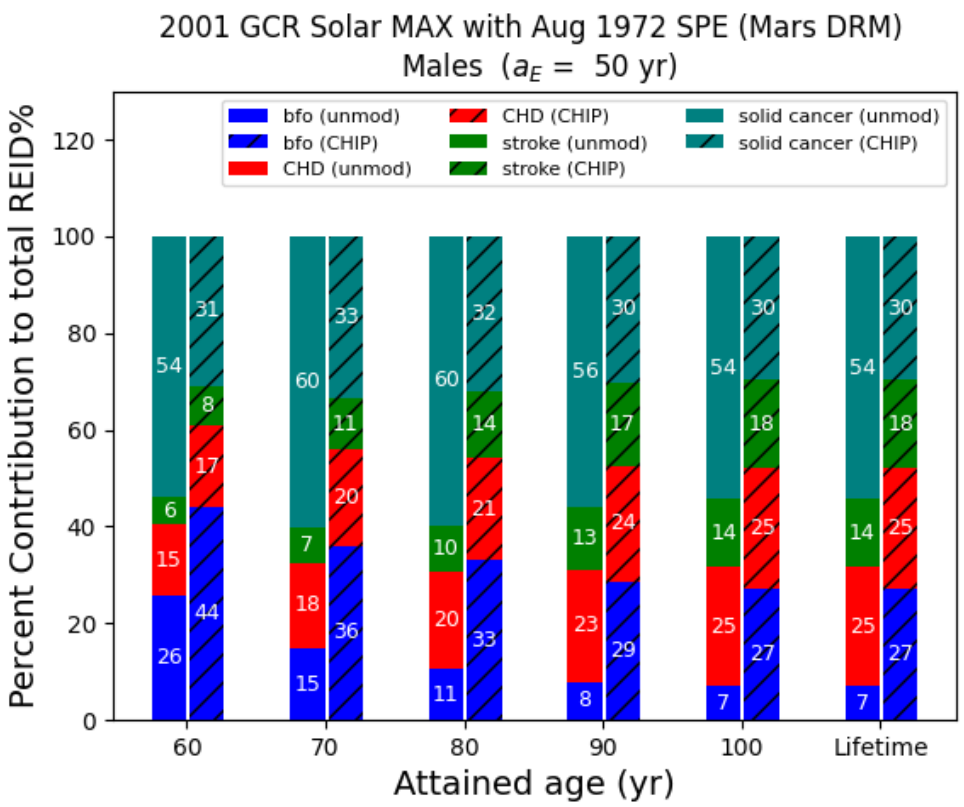


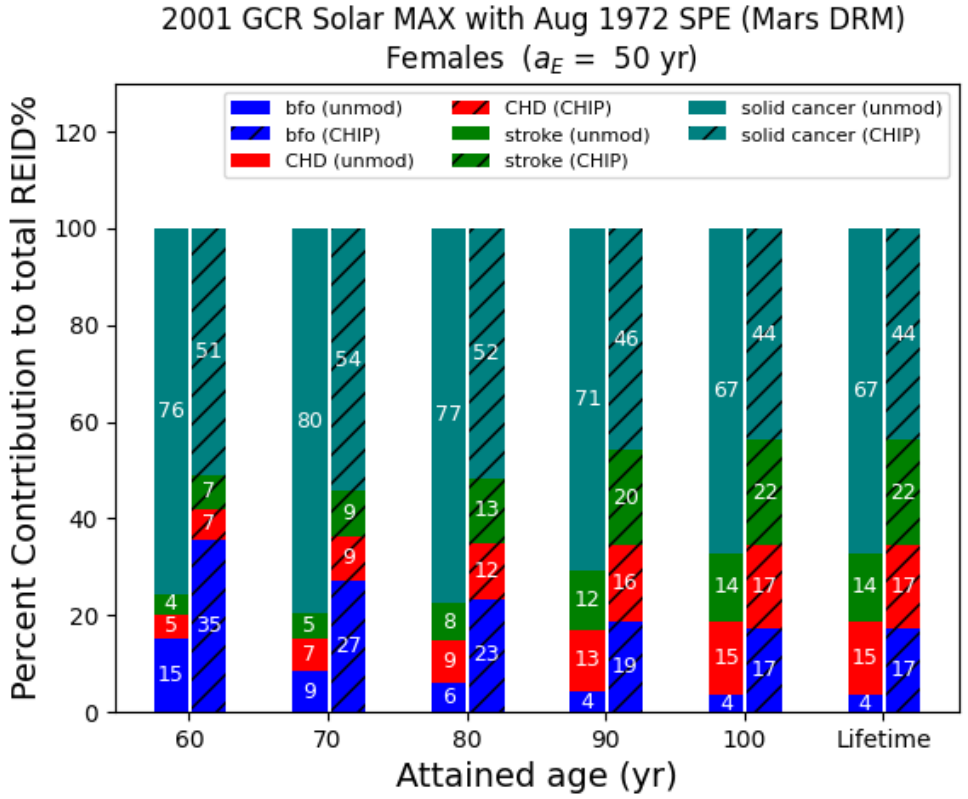




Case 1: Mars Mission without Previous Exposure

*Evaluated from point estimates





Leukemia : NASA Space Cancer Risk Model (NSCR) uses blood forming organs (bfo), where Leukemia originates

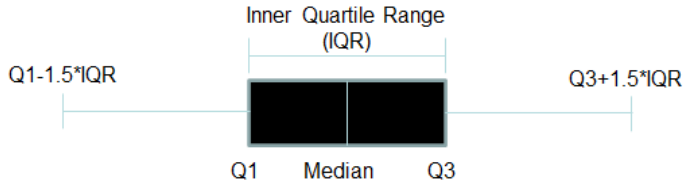
Case 1: Mars Mission without Previous Exposure

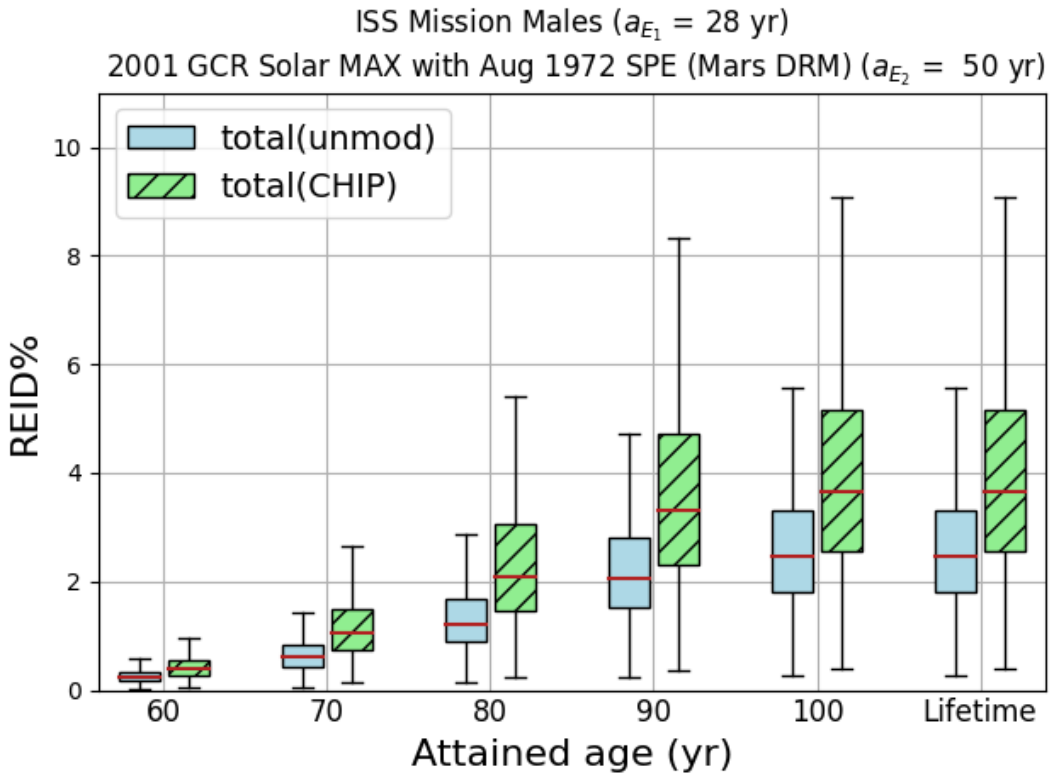
Inflight Risk from Radiation Exposure

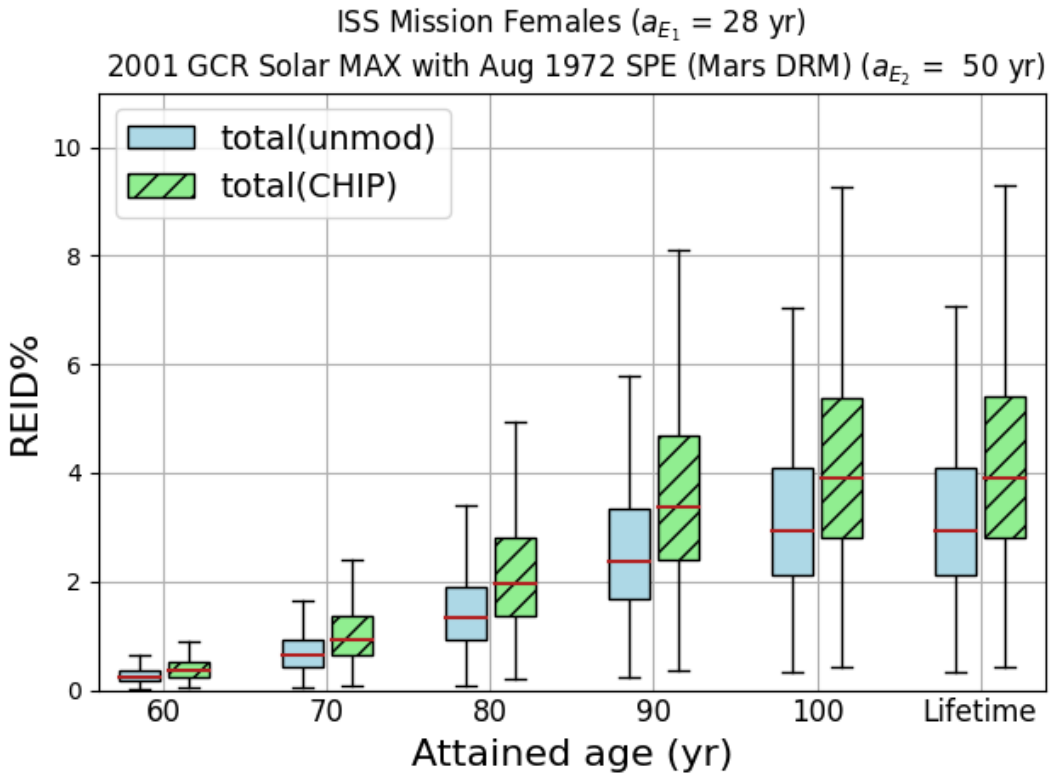
- **Latency in the NASA Space Cancer Risk Model**
  bfo: 2 years
  Solid cancers, stroke, CHD: 5 years

- **Since mission duration is less than 2 years, there is no excess radiation risk (REID% =0)**

Case 2: Mars Mission with Previous Exposure

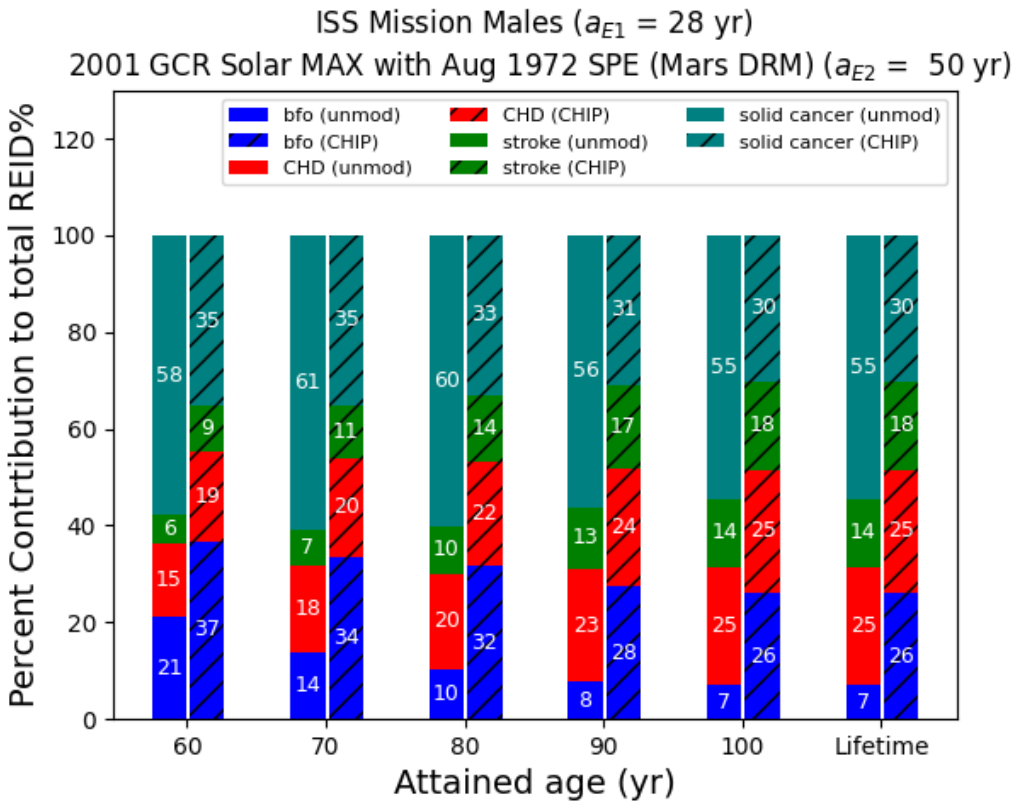


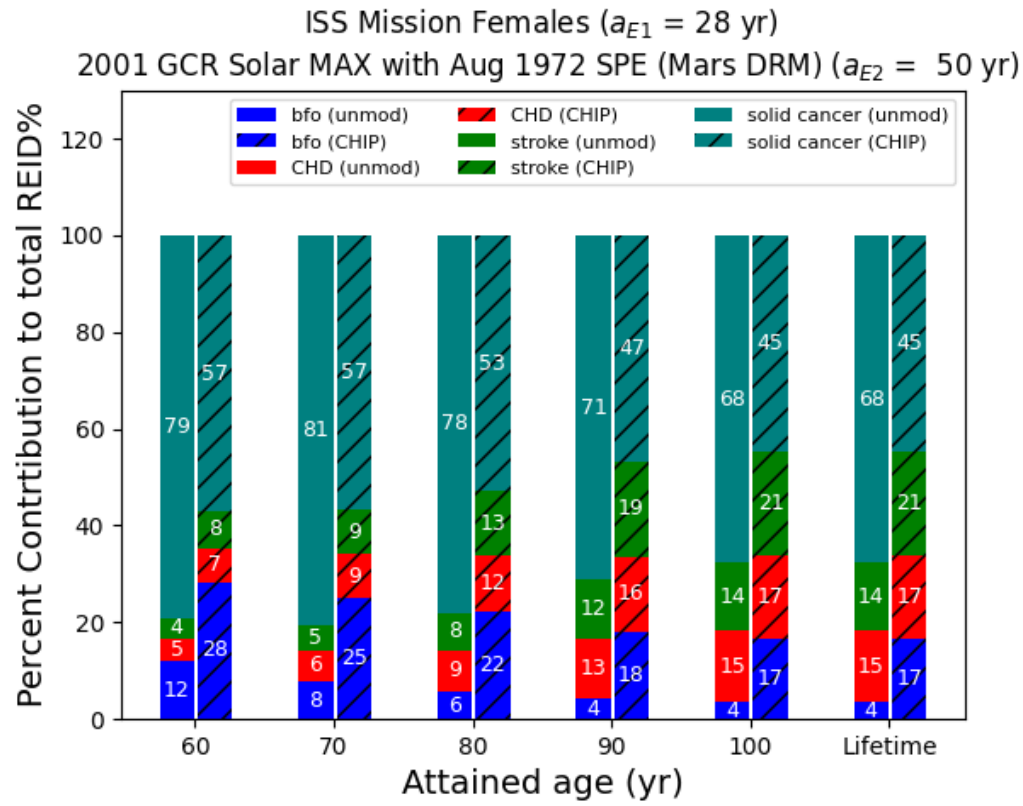




Case 2: Mars Mission with Previous Exposure

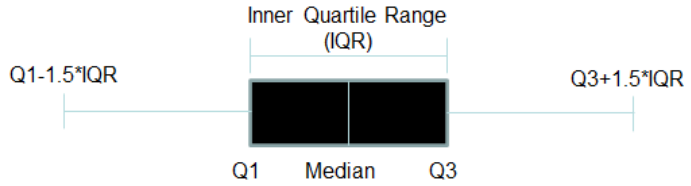
*Evaluated from point estimates

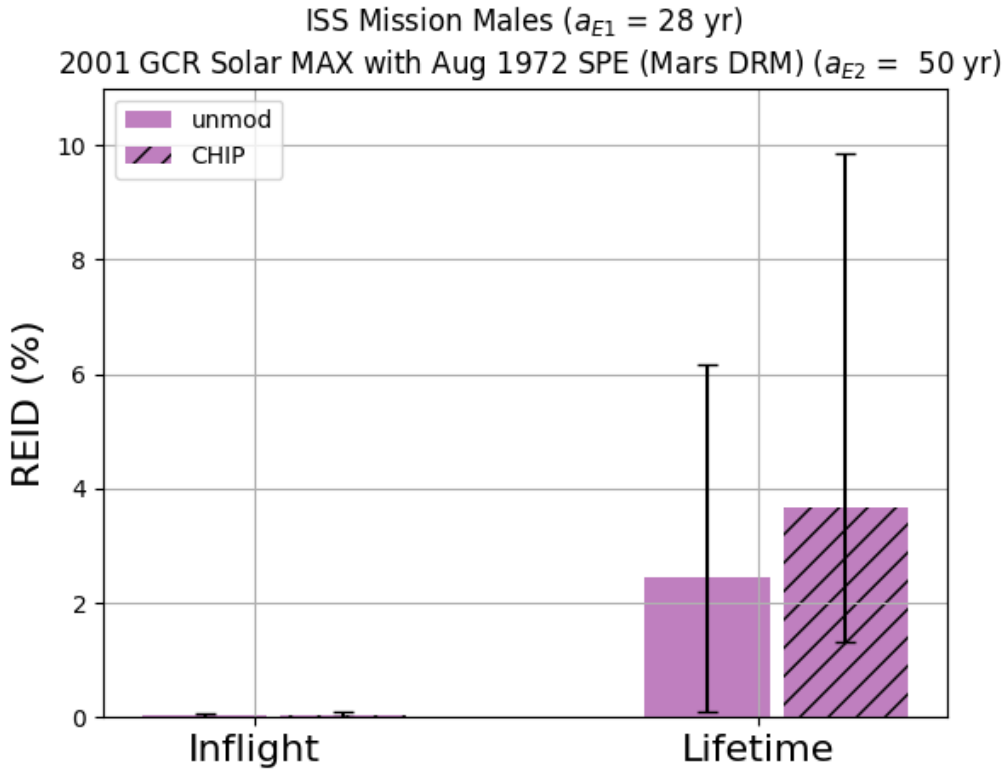


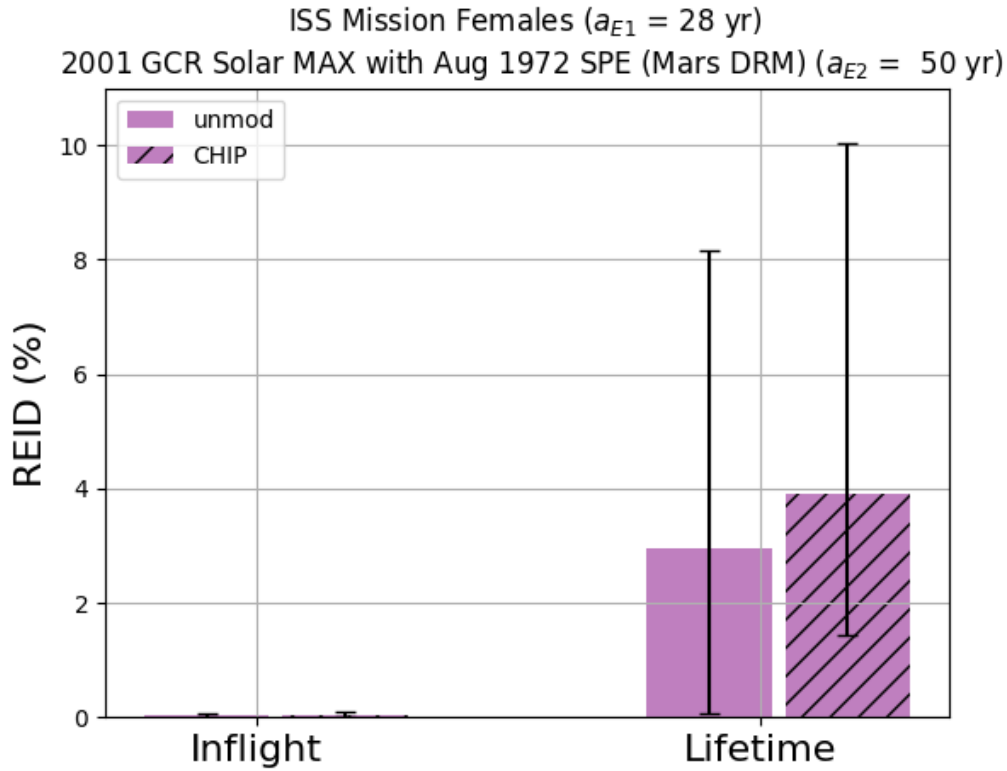


Leukemia : NASA Space Cancer Risk Model (NSCR) uses blood forming organs (bfo), where Leukemia originates

Case 2: Mars Mission with Previous Exposure







Inflight risk from radiation exposure is negligible

Summary

- Inflight risk for CHIP carriers from radiation exposure is negligible
- Even though the infight risk from radiation exposure is small, the **baseline risk** for CHIP carriers remains high
- Males with CHIP have larger risk from leukemia, stroke, and CHD (combined) than from solid cancer for all ages after radiation exposure
- Females with CHIP have larger *lifetime risk* from leukemia, stroke, and CHD (combined) than from solid cancer
- Large increase in total lifetime REID% for males (~45%) and females (~26%) with CHIP
- This study shows that personalized information in risk calculations could be used for medical management